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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/453,350	05/30/95	HELDIN C	0054.009

HM12/0804

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EXAMINER	
SAOUD, C	
ART UNIT	**PAPER NUMBER**
1646	42

DATE MAILED: 08/04/99

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trad marks

Office Action Summary

Application No.	Applicant(s)
08/453,350	HELDIN et al.
Examiner	**Group Art Unit**
Christine Saoud	1646

☒ Responsive to communication(s) filed on *Jun 21, 1999* .

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *25-27 and 43-66* is/are pending in the application.

Of the above, claim(s) *46-54* is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *25-27, 43-45, and 55-66* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____ .

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

— SEE OFFICE ACTION ON THE FOLLOWING PAGES —

DETAILED ACTION

Transitional After Final Practice

1. Since this application is eligible for the transitional procedure of 37 CFR 1.129(a), and the fee set forth in 37 CFR 1.17(r) has been timely paid, the finality of the previous Office action is hereby withdrawn pursuant to 37 CFR 1.129(a). Applicant's second submission after final filed on 21 June 1999 has been entered.

Response to Amendment

2. Claims 25-27 have been amended and claims 58-66 have been added as requested in the amendment of paper #41, filed 21 June 1999. Claims 25-27 and 43-66 are pending in the instant application. Claims 46-54 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b) as being drawn to a non-elected invention (see paper #31, paragraph #3).

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

4. Any objection or rejection of record which is not expressly repeated in this action has been overcome by Applicant's response and withdrawn.

5. Applicant's arguments filed 21 June 1999 have been fully considered but they are not deemed to be persuasive.

Claim Rejections - 35 USC § 102

6. Claims 25-27 and 43-45, 55-57 remain rejected and newly submitted claims 58-66 are rejected under 35 U.S.C. 102(b) as being anticipated by Heldin et al. (Nature 319: 511-514, 1986) for the reasons of record in paper #31 as applied to claims 25-27 and 43-45.

Applicant argues at page 6 of the response that paragraph 2 of the Cousens' Declaration indicates that "none of the above criteria can be used to support the conclusion that Heldin's preparation was free from human proteins other than the ODGF protein". The evidence or "criteria" which was used to support the conclusion in question is that (1) the protein of Heldin appeared to be homogeneous due to a single band on a silver-stained gel, (2) Heldin's statement that one homogeneous component was obtained, and (3) that no other amino acid sequences were obtained from the purified protein preparation.

Applicant first argues Cousens' statements in paragraph 3 of the Declaration which indicate that no protein purification technique can render a preparation which is absolutely homogeneous and lacking in other human proteins. However, Applicant is applying absolutes which are not possible in any preparation, be it from a tissue source or from recombinant production of a protein. This is because in any protein preparation, there will always be trace amounts of human proteins, even if they come from handling of the labware which is used in

making the protein. Applicant's standard of "free of other human proteins" is an unattainable standard which cannot even be met by Applicant's recombinant methods of production. In the preparation of PDGF A-chain homodimer in CHO cells, yeast, or even *E. coli* (in which yeast extract is used as a nutrient), there will always be trace amounts of at least ubiquitin, which is a protein that is found in all eucaryotes. This protein is identical in all eucaryotes, therefore, it would constitute a human protein, regardless of the source, and therefore, would be a contaminant in Applicant's composition. For the purposes of patentability, "free of other human proteins" refers to purity which is judged by conventionally detectable means, such as those that were used in the Heldin et al. reference. Therefore, Applicant's arguments regarding absolute homogeneity are not persuasive because it is a standard which is not attainable by any method in the prior art or in the instant application, absent evidence to the contrary.

Applicant argues at page 7 that many proteins do not stain on a silver stained gel. This may be a fact, however, this is not the only evidence that was considered when determining the purity of the composition of the prior art. Applicant states that "the absence of protein bands on a silver-stained gel is not at all indicative that contaminating human proteins were in fact absent". However, no evidence that there were contaminating present on the gel has been offered in rebuttal, therefore, it would appear that there were no other proteins present in the absence of any additional staining.

Applicant argues spanning pages 7-8 that viral contaminants are difficult to detect, and that it is possible that viral contaminants were present. This may be true, but it is just as possible

that viral contaminants were not present, and in the absence of evidence to the contrary, the facts of record support the conclusion that the protein was homogeneous and without contaminant according to conventional detectable means. Applicant's assertion that the cell line from which the protein of Heldin et al. was isolated could have contained viruses is noted, but unsupported by any facts of record.

Applicant argues at page 8 that "because no other amino acid sequence was obtained from the Heldin preparation does not mean that contaminants were absent" because N-terminal sequencing will not detect blocked amino termini. Even though this is true, there is no evidence to support the conclusion that any such proteins were present in the composition of Heldin et al.

Applicant concludes that "it is evidence that Heldin's preparation cannot be free of human protein contaminants" (see bottom of page 8). However, as stated above, according to Applicant's standard of "free of human protein contaminants", there is no preparation in existence that would meet this standard. According to the facts of record, there is no evidence to support a conclusion that there were any other proteins present in the preparation of Heldin et al. and no evidence of any other protein present has bee provided by Applicant. Attacking the method of purification for potential pitfalls that may have occurred to lead to contamination is not sufficient to demonstrate the presence of an impurity. The opinions and statements made in the Declarations have been considered, but they do not provide evidence of any contaminants in the preparation of Heldin et al. and surely do not support a conclusion that there is an impurity present in the preparation for the purposes of patentability.

Applicant argues that the preparations of claims 55-57 distinguish over the prior art because the preparations of the prior art are not pure and are not in a pharmaceutical carrier acceptable for topical administration. The issue of purity has been considered above. With regard to the presence of a pharmaceutical carrier, the methods, listed under Figure 1 indicate that the purified composition, prior to gel electrophoresis, contained growth promoting activity. This activity was measured on human foreskin fibroblast, which would require the composition to be in a pharmaceutically acceptable carrier for administration to these cells, absent evidence to the contrary. Therefore, the limitations of the claims are met by Heldin et al.

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. Claims 55-57 are rejected under 35 U.S.C. 103(a) as obvious over Heldin et al.

As stated above, it would appear that Heldin et al. anticipates the instant claims directed to pharmaceutical compositions of PDGF A-chain homodimer, wherein the carrier is acceptable for topical administration. Heldin et al. is not clear on whether the purified composition was in a pharmaceutically acceptable carrier prior to the final gel analysis, which confirmed the purity of the composition. However, it would have been prima facie obvious to one of ordinary skill in the

art to dialyze the composition which was eluted from the HPLC column in 0.01M phosphate buffer at pH 7.4 as was previously done in the method in order to obtain a composition in a pharmaceutically acceptable carrier in order to test the biological activity of the composition on human foreskin fibroblasts. One would necessarily need to place the composition in such a carrier in order to administer it to fibroblasts because the high acetic acid concentration from the HPLC column would adversely affect the fibroblasts. Therefore, the invention as a whole would have been prima facie obvious, absent evidence to the contrary.

Conclusion

9. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christine Saoud, Ph.D., whose telephone number is (703) 305-7519. The examiner can normally be reached on Monday to Friday from 8AM to 3PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Paula Hutzell, can be reached on (703) 308-4310. The fax phone number for this Group is (703) 308-0294.

Official papers filed by fax should be directed to (703) 308-4227. Faxed draft or informal communications with the examiner should be directed to (703) 308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

August 2, 1999

CHRISTINE SAOUD
PATENT EXAMINER
Christine Saoud